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EXAMINER	
SANG, HONG	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,918	MULTHOFF, GABRIELE	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,15,21,56 and 57* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15,56 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Multhoff

1. Applicant's election with traverse of Group I (claims 1-8, 15 and 56-57) in the reply filed on 6/24/2009 is acknowledged. The traversal is on the ground(s) that Lindhofer et al. do not teach the production of bispecific molecules wherein one domain binds cell surface membrane-bound HSP protein. Similarly, Takayama et al. do not disclose that the BAG protein may be present on the cell surface membrane of a given cell. Instead, Takayama et al. teach that the BAG protein resides in the nucleus, i.e. inside the cell. It would make no sense to construct a bispecific molecule comprising one binding domain which binds cell surface membrane-bound HSP protein and a second binding domain which binds intracellularly localized BAG protein. The combination of Lindhofer with Takayama is inoperative and destroys the intended function of the claimed invention. Applicant's arguments have been carefully considered but are not persuasive. Takayama et al. disclose that BAG-1 can reside in either the nucleus or the cytosol with the BAG-1L protein apparently having a preference for the nucleus (see page 3123, column 2). Takayama et al. disclose that the shorter BAG-1 protein (36kDa) is the most abundant form of BAG1 found in tumor lines and can bind to Hsp/Hsc70 family proteins and modulate their activities (see page 3122, column 2 and page 3130, right column, paragraph 2). Takayama et al. disclose that BAG-1, BAG-1M and BAG-1L can all interact with Hsc70 (see page 3124 column 1, paragraph 1). Because BAG-1 binds directly to Hsp70 and form complex, it would have been obvious to one skilled in the art to make a bispecific antibody that binds to

both Hsp70 and BAG-1 in order to detect, and/or modulate the formation and function of the Hsp70/BAG-1 complex. While the prior art does not disclose the membrane localization of the Hsp70 and BAG-1, the instant claims are drawn to a product, per se, the bispecific antibody would inherently bind to membrane Hsp70 and BAG-1. For these reasons, the requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-8, 15, 21 and 56-57 are pending. Claims 9-14, 16-20 and 22-55 have been cancelled. Claim 21 is withdrawn from further consideration as being drawn to non-elected inventions.

3. Claims 1-8, 15, 56 and 57 are under examination.

Priority

4. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in EPO on 12/5/2003. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

Specification

5. The disclosure is objected to because of the following informality. The Brief Description of the Drawings does not reference each of the Figures. The Brief Description should be amended to reference Figure 6G. Correction is required.

Claim Objections

6. Claim 57 is objected to because the amino acid residues 158-457 of BAG-4 are not really a C-terminal domain of BAG, although it includes a C-terminal domain.

7. Claims 56 and 57 are objected to because the claims recite specific amino acid residues without reciting the sequence of Hsp70 and Bag-4. The amino acid sequences of Hsp70 and Bag-4 are different in different species. Furthermore, Hsp70 is known in the art as a class of molecular chaperons, each of which has a different amino acid sequence.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 6-7, 15, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites "a bispecific molecule that comprises a first binding domain which binds cell surface membrane-bound heat shock protein (Hsp) and a second binding domain which binds a member of the Bag family". The "binding domain" can be any

molecules that have the function of binding to Hsp or Bag protein, which include antibodies, small molecules, peptides, and proteins. The claims therefore encompass a genus of molecules defined solely by its principal biological property (binding activity), which is simply a wish to know the identity of any material with that biological property. The instant specification only describes antibody or binding fragment thereof that have the recited binding property. Therefore, the written description is not commensurate in scope with the claimed invention. There is insufficient written description regarding "binding domain" because the relevant identifying characteristics of the genus such as structure are not set forth in the specification as-filed, commensurate in scope with the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid,

i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, the limitation "a first binding domain which binds cell surface membrane-bound heat shock protein (Hsp) and a second binding domain which binds a member of the Bag family" does not distinguish any particular molecules from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a "binding domain", one of skill in the art would reasonably conclude that the disclosure of an antibody fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of all "binding domain" having the claimed binding activity. Applicant was only in possession of a bispecific antibody that comprises a first antigen binding site which binds cell surface membrane-bound heat shock protein (Hsp) and a second antigen binding site which binds a member of the Bag

family". See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 112, 1st paragraph

10. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bispecific immunoglobulin of claim 1, wherein the first binding domain is a first immunoglobulin antigen binding site (comprising all 6 CDRs, i.e. HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3), and the second binding domain is a second immunoglobulin antigen binding site (comprising all 6 CDRs, i.e. HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) , does not reasonably provide enablement for a bispecific immunoglobulin of claim 1, wherein the first binding domain is a first immunoglobulin antigen variable region, and the second binding domain is a second immunoglobulin variable region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 5 is rejected because the term "variable region" encompasses V_L alone, V_H alone, or fragments thereof, for example a single CDR.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs

are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA, 1982, Vol 79, page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody having a V_L alone, V_H alone, or a single CDR which contains less than the full complement of CDRs from the heavy and light chain variable regions of an antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional bind domain having a V_H alone, V_L alone, or a CDR. As evidenced by Adair et al. (WO 91/09967A1, Pub. Date: 7/11/1991) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA, 1988, Vol. 85, 3080-3084) demonstrate that a single amino acid substitution of serine for alanine results in

decreased affinity.

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al., Science, 1986, Vol. 233, 747-753).

One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-8, 15, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (US2005/0009033A1, Pub. Date: 1/13/2005, effective filing date: 7/8/2003), in view of Ozawa et al. (Biochem. Biophy. Res. Commun., 2000, 271: 409-413), Goeddel et al. (US 6,110,690, Date of Patent: 8/29/2000), Multhoff (WO 02/22656A2, Pub. Date: 3/21/2002), and Kortt et al. (Biomolecular Engineering, 2001, 18:95-108).

Gray et al. disclose a method of inhibiting proliferation of a breast cancer cell in which BAG4 is amplified and overexpressed, the method comprising contacting the breast cancer cell with a therapeutically effective amount of a BAG4 antibody (see

paragraphs [0009], [0010] and [0134]). Gray et al. teach that the antibody may be a bispecific antibody having biding specificities for at least two different antigens, one of the binding specificities is for BAG4, the other one is for a tumor specific cell-surface protein or receptor (see paragraph [0133]).

Gray et al. do not teach that the other binding specificity of the bispecific antibody is for Hsp70. Gray et al. do not teach that the bispecific antibody binds to the C-terminal regions of BAG4 and Hsp70 at the recited amino acid residues. Gray et al. do not teach that the bispecific antibody is a dimeric molecule. However, these deficiencies are made up for in the teachings of Ozawa, Goeddel, Multhoff and Kortt.

Ozawa et al. disclose that the BAG domain specifically binds and stimulates the ATPase activity of Hsp70/Hsc70 and modulates the function of these molecular chaperones (see page 412, column 2, paragraph 2), and BAG-1 interaction with Hsp70/Hsc70 seems to cause a wide variety of cellular effects, including increase resistance to apoptosis, enhanced cell proliferation, tumor cell migration and metastasis (see page 412, column 2, paragraph 2). Ozawa et al. disclose that Hsp70 is commonly overexpressed in human tumors, and its expression in certain cancer types correlated with poor prognosis, and Hsp70 was also reported to protect tumor cells from TNFα cytotoxicity even in the absence of heat treatment and various other stresses (see page 412, column 2, paragraph 2). Ozawa et al. disclose that besides blocking spontaneous self-association of TNFR-1, SODD (BAG-4) might also act by activating Hsp70/Hsc70 to TNFR-1 and thereby blocking the recruitment of death domain-containing adapter proteins (see page 412, column 2, paragraph 2).

Goeddel et al. teach anti-SODD (BAG-4) specific antibodies including those that bind to carboxyl terminal region at amino acid residues 440-450 of human SODD (see claims).

Multhoff teaches anti-Hsp70 specific Ab that binds to carboxyl terminal at amino acid residues 454-461 of Hsp70 (see page 22, Example 1). Multhoff discloses that said antibody binds selectively to plasma membrane Hsp70 on tumor cells (see Example 1).

Kortt et al. teach that recombinant antibody fragments can be engineered to assemble into stable multimeric oligomer (including multispecific scFv multimers) of high binding avidity and specificity to a wide range of target antigens and haptens (see abstract and page 105). Kortt et al. teach design and expression of diabodies (dimers), triabodies (trimers) and tetrabodies (tetramers) suitable for in vivo imaging and therapy (see abstract). Kortt et al. teach that antibody fragments can be fused with a range of secondary activity domains including radioisotopes for cancer imaging, and toxins for target cell killing (see page 96, paragraph 1). Kortt et al. disclose that the 'biparatopic' reagents or "CRAbs" gain a significant avidity advantage over a single scFv or Fab fragments with obvious advantages for therapy and diagnosis (see page 105, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody that binds to both BAG4 and Hsp70 in view of Gray and Ozawa. One would have been motivated to do so because Ozawa et al teach that the BAG domain specifically binds and stimulates the ATPase activity of Hsp70/Hsc70 and modulates the function of these molecular

chaperones (see page 412, column 2, paragraph 2), and SODD (BAG-4) might also act by activating Hsp70/Hsc70 to TNFR-1 and thereby blocking the recruitment of death domain-containing adapter proteins (see page 412, column 2, paragraph 2). Targeting BAG4 and Hsp70 at same time using a bispecific antibody would be more effective in blocking the function of BAG4 and/or Hsp40 than targeting only one of the two proteins given the fact that the bispecific antibody binds both proteins, and have properties of high binding avidity and specificity. Moreover, Kortt et al. disclose that the 'biparatopic' reagents or "CRAbs" gain a significant avidity advantage over a single scFv or Fab fragments with obvious advantages for therapy and diagnosis (see page 105, column 2). One of ordinary skill in the art would have a reasonable expectation of success to make a bispecific antibody that binds to both BAG4 and Hsp70 because antibodies to BAG4 and Hsp70 were known in the art and methods of making bispecific antibody, dimeric and trimeric antibodies were well known in the art as shown by Kortt.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody that binds to the carboxyl terminal regions of BAG4 and Hsp70 in view of Ozawa and Multhoff. One would have been motivated to do so because Ozawa et al teach that the BAG domain (which is located at the carboxyl terminal region of BAG4) specifically binds and stimulates the ATPase activity of Hsp70/Hsc70 and modulates the function of these molecular chaperones (see page 412, column 2, paragraph 2), and Ozawa et al. teach that the anti-Hsp70 antibody specific to carboxyl terminal region of Hsp70 selectively to plasma membrane Hsp70 on tumor cells. One of ordinary skill in the art would have a

reasonable expectation of success to make a bispecific antibody that binds to the carboxyl terminal regions of BAG4 and Hsp70 because antibodies to the carboxyl terminal regions of BAG4 and Hsp70 were known in the art as shown by Ozawa and Multhoff.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and one would have been motivated to further include a cytotoxic agent or a label to the bispecific antibody for purpose of cancer imaging, and target cell killing (see Kortt, page 96, paragraph 1). One of ordinary skill in the art would have a reasonable expectation of success to further include a cytotoxic agent or a label to the bispecific antibody because such strategy was widely used in the art as shown by Kortt.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643